PRESCRIBING INFORMATION

BACTROBAN OINTMENT®

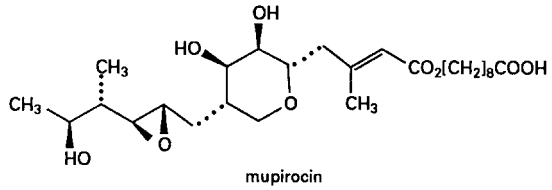
brand of

mupirocin ointment, 2%

For Dermatologic Use

DESCRIPTION

Each gram of Bactroban Ointment (mupirocin ointment), 2% contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment, N.F.) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*E*)-(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The molecular formula of mupirocin is $C_{26}H_{44}O_9$ and the molecular weight is 500.63. The chemical structure is:



mupirocin

CLINICAL PHARMACOLOGY

Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Following intravenous or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, is eliminated by renal excretion, and demonstrates no antibacterial activity. In a study conducted in seven healthy adult male subjects, the elimination half-life after intravenous administration of mupirocin was 20 to 40 minutes for mupirocin and 30 to 80 minutes for monic acid. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no *in vitro* cross-resistance with other classes of antimicrobial agents.

Resistance occurs rarely. However, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-

mediated resistance (MIC >1024 mcg/mL) has been reported in some strains of *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally eight-fold to thirty-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of *Staphylococcus aureus* and *Streptococcus pyogenes*, both *in vitro* and in clinical studies. (See **INDICATIONS AND USAGE**.) The following *in vitro* data are available, BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*.

INDICATIONS AND USAGE

Bactroban Ointment (mupirocin ointment), 2% is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus* and *Streptococcus pyogenes*.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

WARNINGS

Bactroban Ointment is not for ophthalmic use.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of Bactroban Ointment (mupirocin ointment) 2%, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

Bactroban Ointment is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying. A paraffin-based formulation — Bactroban Nasal® (mupirocin calcium ointment) — is available for intranasal use.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, *Bactroban Ointment* should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

Information for Patients: Use this medication only as directed by your healthcare provider. It is for external use only. Avoid contact with the eyes. The medication should be stopped and your healthcare practitioner contacted if irritation, severe itching, or rash occurs.

If impetigo has not improved in 3 to 5 days, contact your healthcare practitioner.

Drug Interactions: The effect of the concurrent application of *Bactroban Ointment* and other drug products has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium *in vitro* and *in vivo* did not indicate a potential for genotoxicity: rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in male and female rats with mupirocin administered subcutaneously at doses up to 14 times a human topical dose (approximately 60 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility and reproductive performance from mupirocin.

Pregnancy
Teratogenic Effects.
Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 22 and 43 times, respectively, the human topical dose (approximately 60 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when *Bactroban Ointment* is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of *Bactroban Ointment* have been established in the age range of 2 months to 16 years. Use of *Bactroban Ointment* in these age groups is supported by evidence from adequate and well-controlled studies of *Bactroban Ointment* in impetigo in pediatric patients studied as a part of the pivotal clinical trials. (See **CLINICAL STUDIES**.)

ADVERSE REACTIONS

The following local adverse reactions have been reported in connection with the use of *Bactroban Ointment* : burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of patients. Systemic reactions to *Bactroban Ointment* have occurred rarely.

DOSAGE AND ADMINISTRATION

A small amount of *Bactroban Ointment* should be applied to the affected area three times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

CLINICAL STUDIES

The efficacy of topical *Bactroban Ointment* in impetigo was tested in two studies. In the first, patients with impetigo were randomized to receive either *Bactroban Ointment* or vehicle placebo t.i.d. for 8 to 12 days. Clinical efficacy rates at end of therapy in the evaluable populations (adults and pediatric patients included) were 71% for *Bactroban Ointment* (n=49) and 35% for vehicle placebo (n=51). Pathogen eradication rates in the evaluable populations were 94% for *Bactroban Ointment* and 62% for vehicle placebo. There were no side effects reported in the group receiving *Bactroban Ointment* .

In the second study, patients with impetigo were randomized to receive either *Bactroban Ointment* t.i.d. or 30 to 40 mg/kg oral erythromycin ethylsuccinate per day (this was an unblinded study) for 8 days. There was a follow-up visit 1 week after treatment ended. Clinical efficacy rates at the follow-up visit in the evaluable populations (adults and pediatric patients included) were 93% for *Bactroban Ointment* (n=29) and 78.5% for erythromycin (n=28). Pathogen eradication rates in the evaluable patient populations were 100% for both test groups. There were no side effects reported in the *Bactroban Ointment* group.

Pediatrics

There were 91 pediatric patients aged 2 months to 15 years in the first study described above. Clinical efficacy rates at end of therapy in the evaluable populations were 78% for *Bactroban Ointment* (n=42) and 36% for vehicle placebo (n=49). In the second study described above, all patients were pediatric except two adults in the group receiving *Bactroban Ointment* . The age range of the pediatric patients was 7 months to 13 years. The clinical efficacy rate for *Bactroban Ointment* (n=27) was 96%, and for erythromycin it was unchanged (78.5%).

HOW SUPPLIED

Bactroban Ointment (mupirocin ointment), 2% is supplied in 22 gram tubes.

NDC 0029-1525-44 (22 gram tube)
Store at controlled room temperature 20° to 25°C (68° to 77°F).

DATE OF ISSUANCE NOV. 2001

GlaxoSmithKline
Research Triangle Park, NC 27709

BC:L12C

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALTABAX safely and effectively. See full prescribing information for ALTABAX.

ALTABAX (retapamulin ointment), 1%
For Dermatological use only
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------

ALTABAX, a pleuromutilin antibacterial, is indicated for the topical treatment of impetigo due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes* in patients aged 9 months or older. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Apply a thin layer of ALTABAX to the affected area (up to 100 cm^2 in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) twice daily for 5 days. (2)
- The treated area may be covered with a sterile bandage or gauze dressing if desired. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

10 mg retapamulin/1g of ointment in 5, 10, 15, and 30 gram tubes (3)

----------CONTRAINDICATIONS----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Discontinue in the event of sensitization or severe local irritation. (5.1)
- Not intended for ingestion. Not for intraoral, intranasal, ophthalmic, or intravaginal use. (5.2)

---------- ADVERSE REACTIONS ----------

The most common drug-related adverse reaction was application site irritation (≤2% of patients). (6)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: June 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

1

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALTABAX® is indicated for use in adults and pediatric patients aged 9 months and older for the topical treatment of impetigo (up to 100 cm^2 in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes [see Clinical Studies (14)]*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ALTABAX and other antibacterial drugs, ALTABAX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

2 DOSAGE AND ADMINISTRATION

A thin layer of ALTABAX should be applied to the affected area (up to 100 cm^2 in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) twice daily for 5 days. The treated area may be covered with a sterile bandage or gauze dressing if desired *[see Patient Counseling Information (17)]*.

3 DOSAGE FORMS AND STRENGTHS

10 mg retapamulin/1g of ointment in 5, 10, 15, and 30 gram tubes

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Irritation

In the event of sensitization or severe local irritation from ALTABAX, usage should be discontinued, the ointment wiped off, and appropriate alternative therapy for the infection instituted *[see Patient Counseling Information (17)]*.

5.2 Not for Systemic or Mucosal Use

ALTABAX is not intended for ingestion or for oral, intranasal, ophthalmic, or intravaginal use. ALTABAX has not been evaluated for use on mucosal surfaces *[see Patient Counseling Information (17)]*. Epistaxis has been reported with the use of ALTABAX on nasal mucosa.

5.3 Potential for Microbial Overgrowth

The use of antibiotics may promote the selection of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Prescribing ALTABAX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The safety profile of ALTABAX was assessed in 2,115 adult and pediatric patients ≥9 months who used at least one dose from a 5-day, twice a day regimen of retapamulin ointment. Control groups included 819 adult and pediatric patients who used at least one dose of the active control (oral cephalexin), 172 patients who used an active topical comparator (not available in the US), and 71 patients who used placebo.

Adverse events rated by investigators as drug-related occurred in 5.5% (116/2,115) of patients treated with retapamulin ointment, 6.6% (54/819) of patients receiving cephalexin, and 2.8% (2/71) of patients receiving placebo. The most common drug-related adverse events (≥1% of patients) were application site irritation (1.4%) in the retapamulin group, diarrhea (1.7%) in the cephalexin group, and application site pruritus (1.4%) and application site paresthesia (1.4%) in the placebo group.

Because clinical studies are conducted under varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Adults: The adverse events, regardless of attribution, reported in at least 1% of adults (18 years of age and older) who received ALTABAX are listed in Table 1.

Table 1. Adverse Events Reported by ≥1% of Adult Patients Treated With ALTABAX in Phase 3 Clinical Studies

Adverse Event	**ALTABAX N = 1,527 %**	**Cephalexin N = 698 %**
Headache	2.0	2.0
Application site irritation	1.6	<1.0
Diarrhea	1.4	2.3
Nausea	1.2	1.9
Nasopharyngitis	1.2	<1.0
Creatinine phosphokinase increased	<1.0	1.0

Pediatrics: The adverse events, regardless of attribution, reported in at least 1% of pediatric patients aged 9 months to 17 years who received ALTABAX are listed in Table 2.

Table 2. Adverse Events Reported by ≥1% in Pediatric Patients Aged 9 Months to 17 Years Treated With ALTABAX in Phase 3 Clinical Studies

Adverse Event	ALTABAX N = 588 %	Cephalexin N = 121 %	Placebo N = 64 %
Application site pruritus	1.9	0	0
Diarrhea	1.7	5.0	0
Nasopharyngitis	1.5	1.7	0
Pruritus	1.5	1.0	1.6
Eczema	1.0	0	0
Headache	1.2	1.7	0
Pyrexia	1.2	<1.0	1.6

Other Adverse Events: Application site pain, erythema, and contact dermatitis were reported in less than 1% of patients in clinical studies.

7 DRUG INTERACTIONS

Co-administration of oral ketoconazole 200 mg twice daily increased retapamulin geometric mean $AUC_{(0-24)}$ and C_{max} by 81% after topical application of retapamulin ointment, 1% on the abraded skin of healthy adult males. Due to low systemic exposure to retapamulin following topical application in patients, dosage adjustments for retapamulin are unnecessary when co-administered with CYP3A4 inhibitors, such as ketoconazole. Based on in vitro P450 inhibition studies and the low systemic exposure observed following topical application of ALTABAX, retapamulin is unlikely to affect the metabolism of other P450 substrates.

The effect of concurrent application of ALTABAX and other topical products to the same area of skin has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Effects on embryo-fetal development were assessed in pregnant rats given 50, 150, or 450 mg/kg/day by oral gavage on days 6 to 17 postcoitus. Maternal toxicity (decreased body weight gain and food consumption) and developmental toxicity (decreased fetal body weight and delayed skeletal ossification) were evident at doses ≥150 mg/kg/day. There were no treatment-related malformations observed in fetal rats.

Retapamulin was given as a continuous intravenous infusion to pregnant rabbits at dosages of 2.4, 7.2, or 24 mg/kg/day from day 7 to 19 of gestation. Maternal toxicity (decreased body weight gain, food consumption, and abortions) was demonstrated at dosages ≥7.2 mg/kg/day (8-fold the estimated maximum achievable human exposure, based on AUC, at 7.2 mg/kg/day). There was no treatment-related effect on embryo-fetal development.

There are no adequate and well-controlled studies in pregnant women. Because animal

reproduction studies are not always predictive of human response, ALTABAX should be used in pregnancy only when the potential benefits outweigh the potential risk.

8.3 Nursing Mothers

It is not known whether retapamulin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALTABAX is administered to a nursing woman. The safe use of retapamulin during breast-feeding has not been established.

8.4 Pediatric Use

The safety and effectiveness of ALTABAX in the treatment of impetigo have been established in pediatric patients 9 months to 17 years of age. Use of ALTABAX in pediatric patients is supported by evidence from adequate and well-controlled studies of ALTABAX in which 588 pediatric patients received at least one dose of retapamulin ointment, 1% *[see Adverse Reactions (6), Clinical Studies (14)]*. The magnitude of efficacy and the safety profile of ALTABAX in pediatric patients 9 months and older were similar to those in adults.

The safety and effectiveness of ALTABAX in pediatric patients younger than 9 months of age have not been established.

8.5 Geriatric Use

Of the total number of patients in the adequate and well-controlled studies of ALTABAX, 234 patients were 65 years of age and older, of whom 114 patients were 75 years of age and older. No overall differences in effectiveness or safety were observed between these patients and younger adult patients.

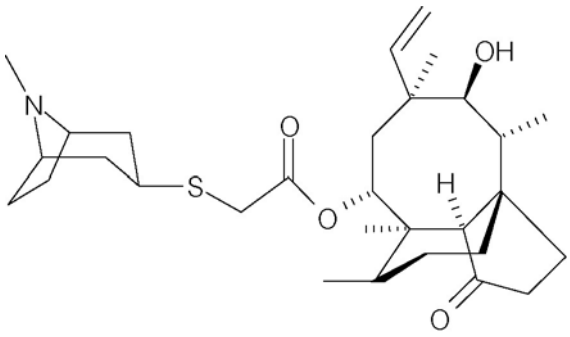
10 OVERDOSAGE

Overdosage with ALTABAX has not been reported. Any signs or symptoms of overdose, either topically or by accidental ingestion, should be treated symptomatically consistent with good clinical practice.

There is no known antidote for overdoses of ALTABAX.

11 DESCRIPTION

ALTABAX contains retapamulin, a semisynthetic pleuromutilin antibiotic. The chemical name of retapamulin is acetic acid, [[(3-*exo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]thio]-, (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl ester. Retapamulin, a white to pale-yellow crystalline solid, has a molecular formula of $C_{30}H_{47}NO_4S$, and a molecular weight of 517.78. The chemical structure is:



Each gram of ointment for dermatological use contains 10 mg of retapamulin in white petrolatum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ALTABAX is an antibacterial agent *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

In post-hoc analyses of manually over-read 12-lead ECGs from healthy subjects (N = 103), no significant effects on QT/QTc intervals were observed after topical application of retapamulin ointment on intact and abraded skin. Due to the low systemic exposure to retapamulin with topical application, QT prolongation in patients is unlikely *[see Clinical Pharmacology (12.3)]*.

12.3 Pharmacokinetics

Absorption: In a study of healthy adult subjects, retapamulin ointment, 1% was applied once daily to intact skin (800 cm^2 surface area) and to abraded skin (200 cm^2 surface area) under occlusion for up to 7 days. Systemic exposure following topical application of retapamulin through intact and abraded skin was low. Three percent of blood samples obtained on Day 1 after topical application to intact skin had measurable retapamulin concentrations (lower limit of quantitation 0.5 ng/mL); thus C_{max} values on Day 1 could not be determined. Eighty-two percent of blood samples obtained on Day 7 after topical application to intact skin and 97% and 100% of blood samples obtained after topical application to abraded skin on Days 1 and 7, respectively, had measurable retapamulin concentrations. The median C_{max} value in plasma after application to 800 cm^2 of intact skin was 3.5 ng/mL on Day 7 (range 1.2 to 7.8 ng/mL). The median C_{max} value in plasma after application to 200 cm^2 of abraded skin was 11.7 ng/mL on Day 1 (range 5.6 to 22.1 ng/mL) and 9.0 ng/mL on Day 7 (range 6.7 to 12.8 ng/mL).

Plasma samples were obtained from 380 adult patients and 136 pediatric patients (aged 2-17 years) who were receiving topical treatment with ALTABAX topically twice daily. Eleven percent had measurable retapamulin concentrations (lower limit of quantitation 0.5 ng/mL), of which the median concentration was 0.8 ng/mL. The maximum measured retapamulin concentration in adults was 10.7 ng/mL and in pediatric patients was 18.5 ng/mL.

Distribution: Retapamulin is approximately 94% bound to human plasma proteins, and the protein binding is independent of concentration. The apparent volume of distribution of

retapamulin has not been determined in humans.

Metabolism: In vitro studies with human hepatocytes showed that the main routes of metabolism were mono-oxygenation and di-oxygenation. In vitro studies with human liver microsomes demonstrated that retapamulin is extensively metabolized to numerous metabolites, of which the predominant routes of metabolism were mono-oxygenation and N-demethylation. The major enzyme responsible for metabolism of retapamulin in human liver microsomes was cytochrome P450 3A4 (CYP3A4).

Elimination: Retapamulin elimination in humans has not been investigated due to low systemic exposure after topical application.

12.4 Microbiology

Retapamulin is a semisynthetic derivative of the compound pleuromutilin, which is isolated through fermentation from *Clitopilus passeckerianus* (formerly *Pleurotus passeckerianus*). In vitro activity of retapamulin against isolates of *Staphylococcus aureus* as well as *Streptococcus pyogenes* has been demonstrated.

Antimicrobial Mechanism of Action: Retapamulin selectively inhibits bacterial protein synthesis by interacting at a site on the 50S subunit of the bacterial ribosome through an interaction that is different from that of other antibiotics. This binding site involves ribosomal protein L3 and is in the region of the ribosomal P site and peptidyl transferase center. By virtue of binding to this site, pleuromutilins inhibit peptidyl transfer, block P-site interactions, and prevent the normal formation of active 50S ribosomal subunits. Retapamulin is bacteriostatic against *Staphylococcus aureus* and *Streptococcus pyogenes* at the retapamulin in vitro minimum inhibitory concentration (MIC) for these organisms. At concentrations 1,000x the in vitro MIC, retapamulin is bactericidal against these same organisms. Retapamulin demonstrates no in vitro target-specific cross-resistance with other classes of antibiotics.

Mechanisms of Decreased Susceptibility to Retapamulin: In vitro, 2 mechanisms that cause reduced susceptibility to retapamulin have been identified, specifically, mutations in ribosomal protein L3 or the presence of an efflux mechanism. Decreased susceptibility of *S. aureus* to retapamulin (highest retapamulin MIC was 2 mcg/mL) develops slowly in vitro via multistep mutations in L3 after serial passage in sub-inhibitory concentrations of retapamulin. There was no apparent treatment-associated reduction in susceptibility to retapamulin in the Phase 3 clinical program. The clinical significance of these findings is not known.

Other: Based on in vitro broth microdilution susceptibility testing, no differences were observed in susceptibility of *S. aureus* to retapamulin whether the isolates were methicillin-resistant or methicillin-susceptible. Retapamulin susceptibility did not correlate with clinical success rates in patients with methicillin-resistant *S. aureus.* The reason for this is not known but may have been influenced by the presence of particular strains of *S. aureus* possessing certain virulence factors, such as Panton-Valentine Leukocidin (PVL). In the case of treatment failure associated with *S. aureus* (regardless of methicillin susceptibility), the presence of strains possessing additional virulence factors (such as PVL) should be considered.

Retapamulin has been shown to be active against the following microorganisms, both in

vitro and in clinical trials *[see Indications and Usage (1)]*.

Aerobic and Facultative Gram-Positive Bacteria:

Staphylococcus aureus (methicillin-susceptible isolates only)

Streptococcus pyogenes

Susceptibility Testing: The clinical microbiology laboratory should provide cumulative results of the in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Susceptibility Testing Techniques:

Dilution Techniques: Quantitative methods can be used to determine the minimum inhibitory concentration (MIC) of retapamulin that will inhibit the growth of the bacteria being tested. The MIC provides an estimate of the susceptibility of bacteria to retapamulin. The MIC should be determined using a standardized procedure.[1,2] Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of retapamulin powder.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations.[2,3] This procedure uses paper disks impregnated with 2 mcg of retapamulin to test the susceptibility of microorganisms to retapamulin.

Susceptibility Test Interpretive Criteria: In vitro susceptibility test interpretive criteria for retapamulin have not been determined for this topical antimicrobial. The relation of the in vitro MIC and/or disk diffusion susceptibility test results to clinical efficacy of retapamulin against the bacteria tested should be monitored.

Quality Control Parameters for Susceptibility Testing: In vitro susceptibility test quality control parameters were developed for retapamulin so that laboratories that test the susceptibility of bacterial isolates to retapamulin can determine if the susceptibility test is performing correctly. Standardized dilution techniques and diffusion methods require the use of laboratory control microorganisms to monitor the technical aspects of the laboratory procedures. Standard retapamulin powder should provide the following MIC and a 2 mcg retapamulin disk should produce the following zone diameters with the indicated quality control strains in Table 3.

Table 3. Acceptable Quality Control Ranges for Retapamulin

Microorganism	MIC Range (mcg/mL)	Disk Diffusion Zone Diameter (mm)
Staphylococcus aureus ATCC 29213	0.06-0.25	NA
Staphylococcus aureus ATCC 25923	NA	23-30
Streptococcus pneumoniae ATCC 49619	0.06-0.5[a]	13-19[b]

NA = Not applicable.

[a] This quality control range is applicable using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

[b] This quality control limit is applicable using Mueller-Hinton agar with 5% sheep blood.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with retapamulin.

Retapamulin showed no genotoxicity when evaluated in vitro for gene mutation and/or chromosomal effects in the mouse lymphoma cell assay, in cultured human peripheral blood lymphocytes, or when evaluated in vivo in a rat micronucleus test.

No evidence of impaired fertility was found in male or female rats given retapamulin 50, 150, or 450 mg/kg/day orally.

14 CLINICAL STUDIES

ALTABAX was evaluated in a placebo-controlled study that enrolled adult and pediatric patients 9 months of age and older for treatment of impetigo up to 100 cm^2 in total area (up to 10 lesions) or a total body surface area not exceeding 2%. The majority of patients enrolled (164/210, 78%) were under the age of 13. The study was a double-blind, randomized, multi-center, parallel-group comparison of the safety of ALTABAX and placebo ointment, both applied twice daily for 5 days. The study was randomized 2 ALTABAX to 1 placebo patient. Patients with underlying skin disease (e.g., preexisting eczematous dermatitis) or skin trauma, with clinical evidence of secondary infection were excluded from these studies. In addition, patients with any systemic signs and symptoms of infection (such as fever) were excluded from the study. Clinical success was defined as the absence of treated lesions, or treated lesions had become dry without crusts with or without erythema compared to baseline, or had improved (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy was required. The intent-to-treat clinical (ITTC) population consisted of all randomized patients who took at least 1 dose of study medication. The clinical per protocol (PPC) population included all ITTC patients who satisfied the inclusion/exclusion criteria and subsequently adhered to the protocol. The intent-to-treat bacteriological (ITTB) population consisted of all randomized patients who took at least one dose of study medication

and had a pathogen identified at study entry. The bacteriological per protocol (PPB) population included all ITTB patients who satisfied the inclusion/exclusion criteria and subsequently adhered to the protocol.

The following table describes the results for clinical response at end of therapy (2 days after treatment) and follow-up (9 days after treatment), by analysis population:

Table 4. Clinical Response at End of Therapy and at Follow-Up by Analysis Population

Analysis Population	ALTABAX		Placebo		Difference in Success Rates (%)	95% CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
End of Therapy						
PPC	111/124	89.5	33/62	53.2	36.3	(22.8, 49.8)
ITTC	119/139	85.6	37/71	52.1	33.5	(20.5, 46.5)
PPB	96/107	89.7	26/52	50.0	39.7	(25.0, 54.5)
ITTB	101/114	88.6	28/57	49.1	39.5	(25.2, 53.7)
Follow-Up						
PPC	98/119	82.4	25/58	43.1	39.2	(24.8, 53.7)
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)
PPB	86/102	84.3	18/48	37.5	46.8	(31.4, 62.2)
ITTB	91/114	79.8	19/57	33.3	46.5	(32.2, 60.8)

n = number with clinical success outcome, N = number in analysis population, PPC = Clinical Per Protocol Population, ITTC = Clinical Intent to Treat Population, PPB = Bacteriological Per Protocol Population, ITTB = Bacteriological Intent to Treat Population

The following table describes the clinical success at end of therapy and follow-up by baseline pathogen:

Table 5. Clinical Response at End of Therapy and Follow-Up for Patients With *Staphylococcus aureus* and *Streptococcus pyogenes* at Baseline in the Per Protocol Bacteriological Population (PPB)

	ALTABAX		Placebo	
Pathogen	**n/N**	**Success Rate (%)**	**n/N**	**Success Rate (%)**
End of Therapy				
Staphylococcus aureus (Methicillin-susceptible)	79/88	89.8	25/48	52.1
Streptococcus pyogenes	29/32	90.6	3/7	42.9
Follow-Up				
Staphylococcus aureus (Methicillin-susceptible)	71/84	84.5	19/44	43.2
Streptococcus pyogenes	29/32	90.6	2/6	33.3

n/N = number of clinical successes/number of pathogens isolated at baseline.

Examination of age and gender subgroups did not identify differences in response to ALTABAX among these groups. The majority of patients entered into this study were classified as White/Caucasian or of Asian heritage; when response rates by racial subgroups were viewed across studies, differences in response to ALTABAX were not identified.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI) Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved Standard. CLSI Document M7-A7. CLSI, Wayne, PA, Jan. 2006.
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing – 17th Informational Standard. M100-S17. CLSI, Wayne, PA, Jan. 2007.
3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Susceptibility Tests. Approved Standard. CLSI Document M2-A9. CLSI, Wayne, PA, Jan. 2006.

16 HOW SUPPLIED/STORAGE AND HANDLING

ALTABAX is supplied in 5 gram, 10 gram, 15 gram and 30 gram tubes.
NDC 0007-5180-05 (5 gram tube)
NDC 0007-5180-10 (10 gram tube)
NDC 0007-5180-22 (15 gram tube)
NDC 0007-5180-25 (30 gram tube)
Store at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

Patients using ALTABAX and/or their guardians should receive the following information and instructions:

- Use ALTABAX as directed by the healthcare practitioner. As with any topical medication, patients and caregivers should wash their hands after application if the hands are not the area for treatment.
- ALTABAX is for external use only. Do not swallow ALTABAX or use it in the eyes, on the mouth or lips, inside the nose, or inside the female genital area.
- The treated area may be covered by a sterile bandage or gauze dressing, if desired. This may also be helpful for infants and young children who accidentally touch or lick the lesion site. A bandage will protect the treated area and avoid accidental transfer of ointment to the eyes or other areas.
- Use the medication for the full time recommended by the healthcare practitioner, even though symptoms may have improved.
- Notify the healthcare practitioner if there is no improvement in symptoms within 3 to 4 days after starting use of ALTABAX.
- ALTABAX may cause reactions at the site of application of the ointment. Inform the healthcare practitioner if the area of application worsens in irritation, redness, itching, burning, swelling, blistering, or oozing.

ALTABAX is a registered trademark of GlaxoSmithKline.

GlaxoSmithKline
Research Triangle Park, NC 27709

June 2010
ALX:3PI

PRESCRIBING INFORMATION

BACTROBAN NASAL®

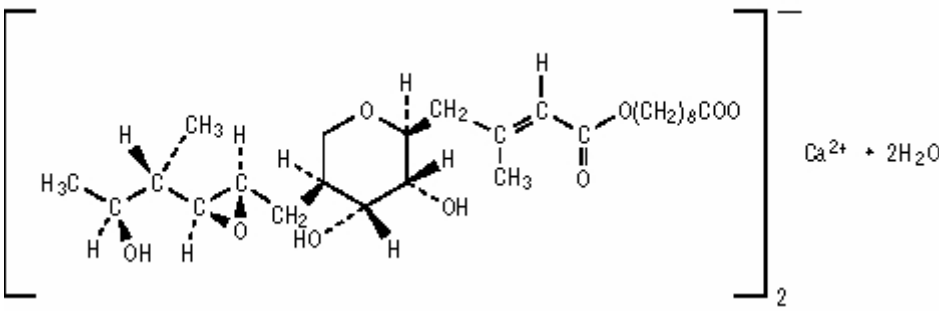
(mupirocin calcium ointment, 2%)

for intranasal use only

DESCRIPTION

BACTROBAN NASAL (mupirocin calcium ointment, 2%) contains the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin. Chemically, it is (α*E*,2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6. The structural formula of mupirocin calcium is:



BACTROBAN NASAL is a white to off-white ointment that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% pure mupirocin free acid) in a soft white ointment base. The inactive ingredients are paraffin and a mixture of glycerin esters (SOFTISAN® 649).

CLINICAL PHARMACOLOGY

Pharmacokinetics: Following single or repeated intranasal applications of 0.2 gram of BACTROBAN NASAL 3 times daily for 3 days to 5 healthy **adult** male subjects, no evidence of systemic absorption of mupirocin was demonstrated. The dosage regimen used in this study was for pharmacokinetic characterization only. (See DOSAGE AND ADMINISTRATION for proper clinical dosing information.)

In this study, the concentrations of mupirocin in urine and of monic acid in urine and serum were below the limit of determination of the assay for up to 72 hours after the applications. The lowest levels of determination of the assay used were 50 ng/mL of mupirocin in urine, 75 ng/mL of monic acid in urine, and 10 ng/mL of monic acid in serum. Based on the detectable limit of the urine assay for monic acid, one can extrapolate that a mean of 3.3% (range: 1.2 to 5.1%) of the applied dose could be systemically absorbed from the nasal mucosa of **adults**.

Data from a report of a pharmacokinetic study in neonates and premature infants indicate that, unlike in adults, significant systemic absorption occurred following intranasal administration of BACTROBAN NASAL in this population. **At this time, the pharmacokinetic properties of mupirocin following intranasal application of BACTROBAN NASAL have not been**

adequately characterized in neonates or other children less than 12 years of age, and in addition, the safety of the product in children less than 12 years of age has not been established.

The effect of the concurrent application of intranasal mupirocin calcium ointment, 2% with other intranasal products has not been studied. (See PRECAUTIONS, Drug Interactions.)

Following intravenous or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, demonstrates no antibacterial activity. In a study conducted in 7 healthy adult male subjects, the elimination half-life after intravenous administration of mupirocin was 20 to 40 minutes for mupirocin and 30 to 80 minutes for monic acid. Monic acid is predominantly eliminated by renal excretion. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this mode of action, mupirocin demonstrates no in vitro cross-resistance with other classes of antimicrobial agents.

When mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1,024 mcg/mL) has been reported in some strains of *Staphylococcus aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved topically by intranasal administration. However, the minimum bactericidal concentration (MBC) against relevant intranasal pathogens is generally 8-fold to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of nasal secretions on the MICs of intranasally applied mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of methicillin-resistant *S. aureus*, both in vitro and in clinical studies of the eradication of nasal colonization. BACTROBAN NASAL only has established clinical utility in nasal eradication as part of a comprehensive program to curtail institutional outbreaks of infections with methicillin-resistant *S. aureus*. (See INDICATIONS AND USAGE.)

The following in vitro data are available, **but their clinical significance is unknown**. Mupirocin exhibits in vitro MICs of 1 mcg/mL or less against most (>90%) strains of methicillin-susceptible *S. aureus*; however, the safety and effectiveness of mupirocin calcium in eradicating nasal colonization of and preventing subsequent infections due to methicillin-susceptible *S. aureus* have not been established.

INDICATIONS AND USAGE

BACTROBAN NASAL is indicated for the eradication of nasal colonization with methicillin-resistant *S. aureus* in adult patients and health care workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high

risk of methicillin-resistant *S. aureus* infection during institutional outbreaks of infections with this pathogen.

NOTE:

1. There are insufficient data at this time to establish that this product is safe and effective as part of an intervention program to prevent autoinfection of high-risk patients from their own nasal colonization with *S. aureus*.
2. There are insufficient data at this time to recommend use of BACTROBAN NASAL for general prophylaxis of any infection in any patient population.
3. Greater than 90% of subjects/patients in clinical trials had eradication of nasal colonization 2 to 4 days after therapy was completed. Approximately 30% recolonization was reported in 1 domestic study within 4 weeks after completion of therapy. These eradication rates were clinically and statistically superior to those reported in subjects/patients in the vehicle-treated arms of the adequate and well-controlled studies. Those treated with vehicle had eradication rates of 5% to 30% at 2 to 4 days post-therapy with 85% to 100% recolonization within 4 weeks.

All adequate and well-controlled trials of this product were vehicle-controlled; therefore, no data from direct, head-to-head comparisons with other products are available at this time.

CONTRAINDICATIONS

BACTROBAN NASAL is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

AVOID CONTACT WITH THE EYES. Application of BACTROBAN NASAL to the eye under testing conditions has caused severe symptoms such as burning and tearing. These symptoms resolved within days to weeks after discontinuation of the ointment.

In the event of a sensitization or severe local irritation from BACTROBAN NASAL, usage should be discontinued.

PRECAUTIONS

General: As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi. (See DOSAGE AND ADMINISTRATION.)

Information for Patients: Patients should be given the following instructions:

- Apply approximately one-half of the ointment from the single-use tube directly into 1 nostril and the other half into the other nostril;
- Avoid contact of the medication with the eyes;
- Discard the tube after using, do not re-use;
- Press the sides of the nose together and gently massage after application to spread the ointment throughout the inside of the nostrils; and
- Discontinue usage of the medication and call your healthcare practitioner if sensitization or severe local irritation occurs.

Drug Interactions: The effect of the concurrent application of intranasal mupirocin calcium and other intranasal products has not been studied. Until further information is known, mupirocin calcium ointment, 2% should not be applied concurrently with any other intranasal products.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium in vitro and in vivo did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in rats with mupirocin administered subcutaneously at doses up to **40** times the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility from mupirocin sodium.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 65 and 130 times, respectively, the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BACTROBAN NASAL is administered to a nursing woman.

Pediatric Use: Safety in children under the age of 12 years has not been established. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Clinical Trials: In clinical trials, 210 domestic and 2,130 foreign adult subjects/patients received BACTROBAN NASAL ointment. Less than 1% of domestic or foreign subjects and patients in clinical trials were withdrawn due to adverse events.

The most frequently reported adverse events in foreign clinical trials were as follows: Rhinitis (1.0%), taste perversion (0.8%), pharyngitis (0.5%).

In domestic clinical trials, 17% (36/210) of adults treated with BACTROBAN NASAL ointment reported adverse events thought to be at least possibly drug-related. The incidence of adverse events that were reported in at least 1% of adults enrolled in domestic clinical trials were as follows:

ADVERSE EVENTS (≥1% INCIDENCE)-ADULTS IN US TRIALS

	% of Subjects/Patients Experiencing Event BACTROBAN NASAL (n=210)
Headache	9%
Rhinitis	6%
Respiratory disorder, including upper respiratory tract congestion	5%
Pharyngitis	4%
Taste perversion	3%
Burning/stinging	2%
Cough	2%
Pruritus	1%

The following events thought possibly drug-related were reported in less than 1% of adults enrolled in domestic clinical trials: Blepharitis, diarrhea, dry mouth, ear pain, epistaxis, nausea, and rash.

All adequate and well-controlled clinical trials have been performed using BACTROBAN NASAL ointment, 2% in 1 arm and the vehicle ointment in the other arm of the study. No adequate and well-controlled safety data are available from direct, head-to-head comparative studies of this product and other products for this indication.

OVERDOSAGE

Following single or repeated intranasal applications of BACTROBAN NASAL to adults, no evidence for systemic absorption of mupirocin was obtained. Intravenous infusions of 252 mg, as well as single oral doses of 500 mg of mupirocin, have been well tolerated in healthy adult subjects. There is no information regarding local overdose of BACTROBAN NASAL or regarding oral ingestion of the nasal ointment formulation.

DOSAGE AND ADMINISTRATION

(See INDICATIONS AND USAGE.)

Adults (12 years of age and older): Approximately one-half of the ointment from the single-use tube should be applied into 1 nostril and the other half into the other nostril twice daily (morning and evening) for 5 days.

After application, the nostrils should be closed by pressing together and releasing the sides of the nose repetitively for approximately 1 minute. This will spread the ointment throughout the nares.

The single-use 1.0 gram tube will deliver a total of approximately 0.5 grams of the ointment (approximately 0.25 grams/nostril).

The tube should be discarded after usage; it should not be re-used.

The safety and effectiveness of applications of this medication for greater than 5 days have not been established. There are no human clinical or pre-clinical animal data to support the use of this product in a chronic manner or in manners other than those described in this package insert.

Until further information is known, BACTROBAN NASAL should not be applied concurrently with any other intranasal products.

HOW SUPPLIED

BACTROBAN NASAL is supplied in 1.0-gram tubes.
NDC 0029-1526-11 (package of 10 single-tube cartons).

Store between 20° and 25°C (68° and 77°F); excursions permitted to 15°-30°C (59°-86°F). Do not refrigerate.

REFERENCE

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Approved Standard. CLSI Document M7-A7. CLSI, Wayne, PA, January 2006.

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